

do not exclude allergy, for positive reactions are not found in those cases with the delayed clinical reaction. In some, eosinophilia is present.

One striking peculiarity of clinical allergy is the frequent repetition of attacks or its distressing chronicity. This is evidenced in practically all the cases cited. Though usually not serious from the standpoint of mortality, allergy may form a serious problem for patient and physician alike unless the cause can be ascertained and removed.

Let us now answer concretely, and I hope in not too unsatisfactory a way, the question asked at the beginning of this paper by saying that gastro-intestinal symptoms do occur as the result of allergies frequently, in my experience, in connection with other allergies, but not necessarily so. The cutaneous tests may help in the diagnosis in a certain percentage of these cases, but to my mind what is even more important is a careful clinical study with the allergic viewpoint in mind.

SIMPLE ACHLORHYDRIC ANEMIA*

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General Considerations:

In recent years, many articles have been published concerning a type of idiopathic microcytic anemia which has been given various names. The simple achlorhydic anemia of Witts (1), Davies (2), Hare (3), Hurst (4), and Haden (5), the cryptogenic achylic chloranemia of Kaznelson, Reimann and Weiner (6), the primary hypochromic anemia of Dameshek (7), and Waugh (8), the idiopathic hypochromemia of Mills (9), the idiopathic secondary anemia of Watkins (10), the simple achylic anemia

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of Meulengracht (11), and the chronic chlorosis of Adamson and Smith (12), all belong to the same clinical syndrome.

Although the association of achlorhydria and pernicious anemia was known for many years previously, Einhorn (13), in 1903, reported 15 cases of gastric anacidity in three of which simple anemia was present. Priority, however, should be credited to Faber (14) for describing the complete clinical picture of simple achlorhydric anemia. Of 112 cases of achylia gastrica reported in 1909, he found 20 cases with secondary anemia of the type under consideration. In 1913 a further communication by Faber (15) reported 207 cases of achylia with 23 simple anemias.

Weinberg (16), in 1920, studied 77 cases of constitutional achylia and found 15 cases (19 per cent) associated with secondary anemia. Faber and Gram (17), in 1924, described an additional 90 cases of achylia with 41 per cent simple anemias.

Weiner and Kaznelson (18), in 1926, reported the first descriptions of bone-marrow sections made at biopsies in these cases. These findings have been substantiated by Witts (1) and Dameshek (7).

The disease is a hypochromic microcytic type of anemia, occurring predominantly in middle-aged women, and usually associated with an achlorhydria or possibly an hypochlorhydria. Its etiology is obscure. Its course is protracted with a tendency to remissions and exacerbations. Excellent results in its treatment have been reported from the use of adequate doses of inorganic iron preparations.

In a survey of all patients with anemia, from whatever cause, examined during the past 5 years, the authors have been able to classify 43 cases as simple achlorhydric anemia. Of these patients 6 developed anemia after gastric surgery, 5 having had partial gastrectomies and the other, a physiological total gastrectomy for carcinoma of stomach. Lues was found as an associated condition in 6 cases.

During the same period a large number of other cases of hypochromic anemia was studied. These differed from the above-mentioned syndrome with respect to age, sex, and the constant presence of hydrochloric acid in the gastric contents. These anemias correspond to chlorosis. There is no doubt that the majority of these also have an associated iron deficiency but in addition some nutritional disturbance as well. Although some patients may present the chronic course of the achlorhydric group, the anemia usually does not recur after treatment particularly in children and young individuals. Such cases will be discussed in more detail in a subsequent communication.

In all the patients, gastric analyses were made by the Rehfuess fractional determination, and the majority of those who showed anacidity were re-examined, using histamine and neutral red. In a small minority of the achlorhydrics there was an absence of pepsin and rennin as well.

Typical blood changes in some of the cases are presented in the table. The normal blood picture and also that of pernicious anemia are included for comparison.

Incidence:

The sex of the patients was predominantly female (80 per cent), only 20 per cent having been males.

Most of the patients were in the fourth and fifth decades of life, the youngest being 20 years of age and the oldest 65.

No particular race or nationality showed any special predisposition; nor did any occupation appear to bear a causal relationship.

Etiology and Pathogenesis:

The underlying cause of simple achlorhydric anemia depends upon a number of factors, viz.: (1) an achlorhydric constitution or the so-called chronic abdominal invalid of Witts (19); (2) iron deficiency; (3) nutritional disturbances; (4) associated complicating conditions.

There is no doubt that the close association of achlorhydria with iron deficiency etiologically segregates the so-called achylic type from other disturbances, and that associated complicating conditions are of slighter consequence in the pathogenesis of this particular group. In the normochlorhydric group (or chlorosis) such complications are possibly more important, causing a greater iron demand and, therefore, producing an iron deficiency.

The more recent opinions regarding the pathogenesis of achlorhydric anemia would seem to incline to an iron deficiency, either as to intake or assimilation. In clinical experiments on achlorhydric patients with anemia Mettier and Minot (20) showed that iron is absorbed best when the reaction of the duodenum and jejunum is acid, and that large doses are necessary for optimal response.

Heath, Strauss and Castle (21) conclude that, "a simple explanation is offered for the effectiveness of iron therapy in certain types of hypochromic anemia, namely, that these types of anemia are due to a deficiency chiefly of iron, preventing adequate hemoglobin formation."

A similar view is expressed by Dameshek (7) who believes that inadequate gastric digestion of iron may lead to faulty hemoglobin synthesis, and thus results in improper maturation of the immature red elements of the bone-marrow.

Davies (2) is of the opinion that iron deficiency arises in achlorhydrics from the ingestion over long periods of concentrated foods because of post prandial discomfort which occurs after the intake of protein foods and vegetables.

In discussing the cases of hypochromic anemia in pregnancy, Strauss (22) and Strauss and Castle (23) conclude that the added demands for hemoglobin during gestation result in an iron deficiency conditioned by gastric anacidity or low acidity.

Witts (1) associates the development of this anemia

with the stress of the reproductive era in women who have some inherent inadequacy of the blood forming system, particularly in the synthesis of hemoglobin. In the induced achlorhydria of gastrectomized patients he believes diet, deficient in iron content, together with poor iron assimilation are important factors in the development of the anemia.

Bloomfield (24) is likewise inclined to believe that because of the predominance of this anemia in females, it is in some way linked to the menstrual function in individuals who have some erythropoetic deficiency, either primary or secondary to faulty diet.

It has been held by some that achlorhydric anemia is closely allied to pernicious anemia. Davies (2) and Zadek (25) describe an intermediate group which falls between these two extremes and which responds to both liver and iron. Gram (26) has reported a family traced through three generations in which pernicious anemia or achlorhydric anemia occurs in different members of the same family. One case was followed from its inception as a hypochromic anemia to a fully developed pernicious anemia. Dameshek (7) believes hypochromic anemia is related in some way to pernicious anemia, of which it may be an abnormal type.

The artificial production of achlorhydria through partial or total gastrectomy may throw additional light on the etiology of hypochromic anemia. Only 5 per cent of our series of 50 cases of subtotal gastrectomy including one total gastrectomy (who has been followed 2 years) developed anemia. These have been hypochromic in type, and in no case has pernicious anemia been observed.

Achlorhydric anemia, therefore, may be regarded as a disturbance of iron metabolism which occurs chiefly in women during the period of sexual maturity.

Symptomatology:

These are variable but patients usually seek aid because of the symptoms arising from the anemia, viz.: weak-

ness, palpitation, dyspnea, and, occasionally, edema of the extremities. Less commonly, soreness of the tongue, paræsthesias, or menorrhagia are the chief complaints. At times gastric disturbances—such as anorexia, nausea, epigastric distress and diarrhea are the chief complaints. Most of the patients regard their illness as of long duration.

The patients present marked evidences of anemia. The color of the skin is somewhat yellowish or waxy. Haden (5) emphasized the importance of the blue sclerae observed in such cases in contradistinction to the yellow sclerae in pernicious anemia. In the more severe cases, hemoglobin below 40 per cent, enlargement of the area of cardiac dullness may be found, and usually an associated hemic murmur is heard. A sub-febrile temperature, so-called anemic fever, may likewise be observed. In some instances the temperature may be considerably increased—as high as 103° to 104°. Atrophy of the papillae of the tongue is occasionally present. Palpable liver and spleen are observed less constantly. Loss in weight occurs in a considerable number of cases. In the hypochromic cases, an unusual finding is the brittleness of the nails, and even koilonychia or spoon nails, which are frequently noticed by the patients themselves.

The combination of fever and a cardiac murmur in one patient with hemoglobin of 18 per cent led to the diagnosis of subacute bacterial endocarditis. Marked improvement occurred with iron medication. With the improvement of the blood status, the fever and cardiac signs disappeared.

Hematological Findings:

The blood picture (See Table) is characterized by severe or moderately severe secondary anemia associated with low color index (usually 0.5 or below). The proportionate reduction of the hemoglobin is therefore greater than of the red cells. The lowest hemoglobin was 18 per cent with red cell count of 1,830,000. The color index varied from 0.5 to 0.7.

Case No.	Name	Sex	Age	Associated condition	Hemo-globin %	Red blood cells	White blood cells	Platelets
1.	M.M.	F	38	Nasal polypi	32	3,650,000	6,600	300,000
2.	L.S.	F	42	None	36	4,000,000	6,900	220,000
3.	R.S.	F	70	None	40	5,010,000	8,400	330,000
4.	R.K.	F	54	None	63	4,400,000	6,400	230,000
5.	E.R.	F	45	None	30	3,420,000	6,450	100,000
6.	N.R.	F	44	None	24	2,600,000	8,100	250,000
7.	M.B.	F	17	None	54	4,600,000	7,800	400,000
8.	G.S.	F	46	Menorrhagia	45	4,200,000	6,000	360,000
9.	M.C.	F	24	Uncinariasis	38	2,970,000	5,900	250,000
10.	A.B.	F	23	Lues	18	1,830,000	3,200	130,000
11.	Y.Z.	F	48	Lues	26	2,560,000	8,000	550,000
12.	A.P.	M	64	Lues; Gastric ulcer	32	1,850,000	8,500	220,000
13.	R.G.	M	51	Gastric carcinoma; Total gastrectomy	66	4,200,000	5,100	260,000
14.	R.L.	F	47	Gastric ulcer; Partial gastrectomy	64	5,270,000	5,400	145,000
15.	B.G.	M	35	Gastric ulcer; Partial gastrectomy	50	4,350,000	8,000	280,000
16.	B.S.	M	26	Normal	90	4,850,000	9,250	400,000
17.	B.B.	M	34	Normal	97	5,600,000	7,400	310,000
18.	C.S.	F	45	Normal	93	5,050,000	8,600	380,000
19.	C.B.	M	54	Pernicious Anemia	60	2,100,000	7,000	100,000

Polymorphonuclears nonseg- mented	seg- mented	eosino- phil	baso- phil	Lympho- cytes	Mono- cytes	Volume packed red cells c.c. per 100 c.c.	Volume % of normal	Color index	Mean diameter or red blood cells in micra
% 2	% 57	% 3	% 1	% 37	% 0	19	0.41	0.44	6.0
8	51	0	0	32	9	23	0.50	0.45	6.2
2	64	2	1	22	9	25	0.54	0.4	5.9
3	51	1	1	36	8	33	0.72	0.7	6.3
4	61	1	0	26	8	19	0.41	0.45	5.8
8	58	0	0	28	6	22	0.49	0.5	5.8
2	64	1	0	30	3	30	0.65	0.6	6.0
0	49	3	0	44	4	23	0.50	0.5	6.0
14	59	6	0	16	5	25	0.54	0.7	6.55
13	63	1	0	15	8	16	0.35	0.5	6.3
3	47	4	0	38	8	15	0.33	0.52	6.25
9	81	3	0	3	4	20	0.48	0.89	7.2
2	60	3	1	27	7	35	0.76	0.78	7.0
4	50	2	0	36	8	32	0.69	0.61	6.3
2	64	1	0	31	2	32	0.69	0.58	6.24
9	63	2	0	25	1	44	0.95	0.9	7.4
5	56	2	0	33	4	46	1.0	0.87	7.5
2	60	2	0	30	6	45	0.97	0.93	7.4
1	60	2	0	34	3	26	0.56	1.5	8.1

Although the hemoglobin, red cell count and color index are indicative of the type of anemia, other important findings are of value. The average diameter of red cells determined by the method of Price-Jones (27) (Chart 1) is usually well below 7.0 micra, and the mean diameter varies between 5.5 micra and 6.5 micra. Diameter of the red cells in other types of hypochromic anemia (i.e., with free hydrochloric acid) and in this variety of anemia associated with lues, shows a tendency to larger sized red cells (See Table). In the former, they may reach a mean diameter of 7.0 micra, and in the latter the diameter was as high as 7.2 micra.

This diminution in the size of the red blood-cells (Figs. 1 and 2) is accompanied by a proportionate diminution in average relative cell volume. The normal volume of the packed red cells is 46 c.c. per 100 c.c. of blood. The volume of red cells in this type of anemia is considerably diminished

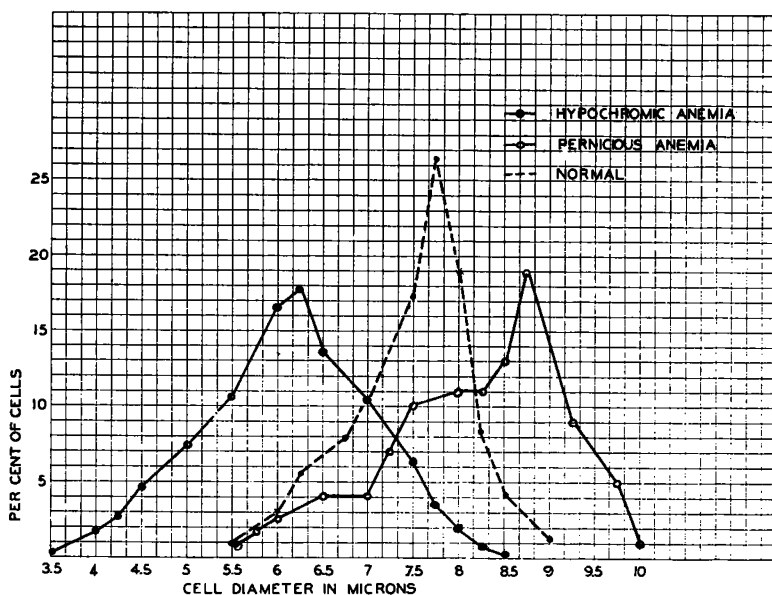


Chart 1. Price-Jones Curves in Simple Achlorhydic Anemia Compared with Pernicious Anemia and the Normal Curve. The Mean Diameter of Red Cells—Simple Achlorhydic Anemia 6.0, Normal 7.5, Pernicious An-

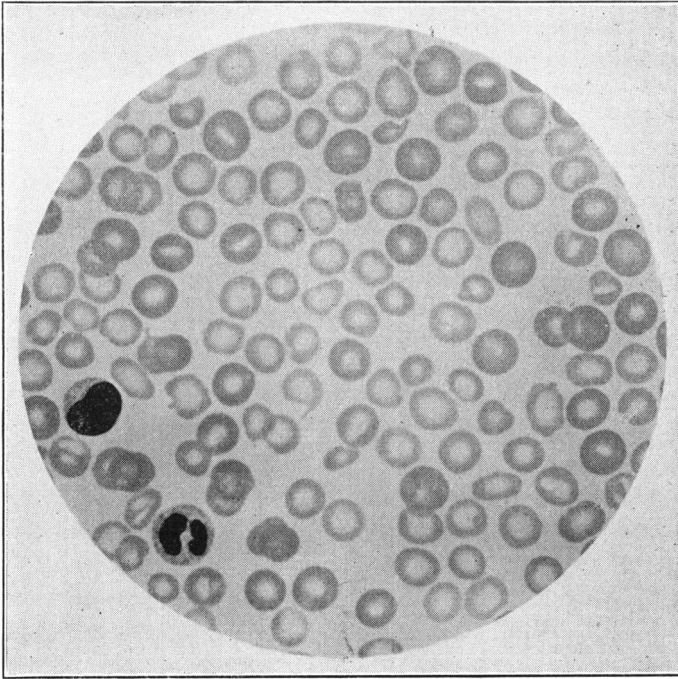


Fig. 1. Blood Smear in Simple Achlorhydric Anemia (Luetic) Following Blood Transfusion. Note the Microcytosis in Comparison with the Normal Transfused Cells. (X 1000).

(See Table). In the author's series, variation from 19 c.c. to 37 c.c. occurred, or in relation to the average normal volume from 41 per cent to 81 per cent. Similarly, there is also a diminution of the mean corpuscular volume (Wintrobe (28)), and of the volume index (Capps (29)).

This microcytosis of the red blood-cells is well demonstrated after blood transfusions (Fig. 1), or by superimposing the blood smear from an hypochromic anemia on that from a normal patient.

In the blood smear, the red cells are found to be definitely hypochromatic (Fig. 2). There is marked increase in size of the central pale area, so that the hemoglobin is concentrated or piled up at the periphery in most of the small

red cells (anachromasia). Few cells appear normal (orthochromasia). In the very severe anemias, marked poikilocytosis occurs.

The reticulocytes are either normal or absent. The fragility of the red cells is usually normal. Occasionally, an increase of the minimal fragility may occur especially after pregnancy and in the rare type with dysphagia (Vinson Plummer syndrome, 30).

The number of white blood-cells is either normal or considerably diminished. The differential blood picture of the leucocytes is usually normal. Occasionally, a slight eosinophilia is found. The size of the polymorphonuclear cells is normal in contradistinction to their increase in size in pernicious anemia.

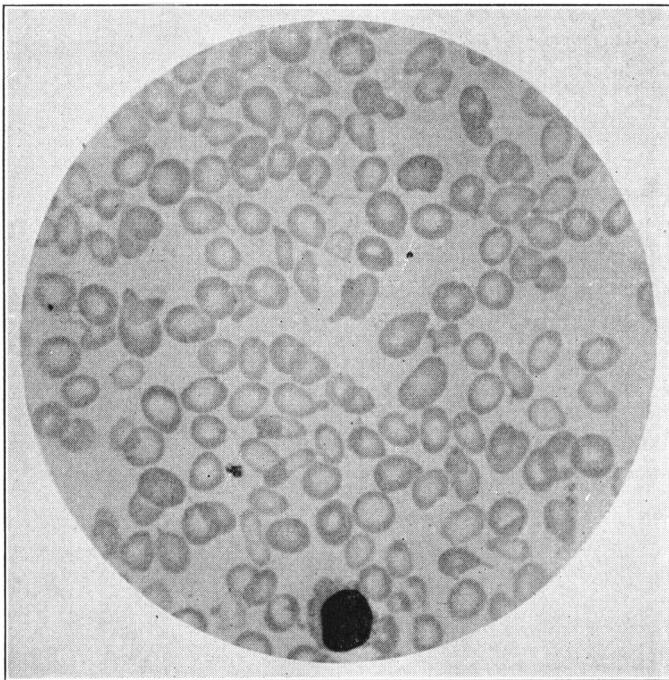


Fig. 2. Blood Smear. Achlorhydric Anemia. Anisocytosis, Poikilocytosis Generalized Microcytosis, and Anachromasia (Hemoglobin 32 Per Cent). (X 1000).

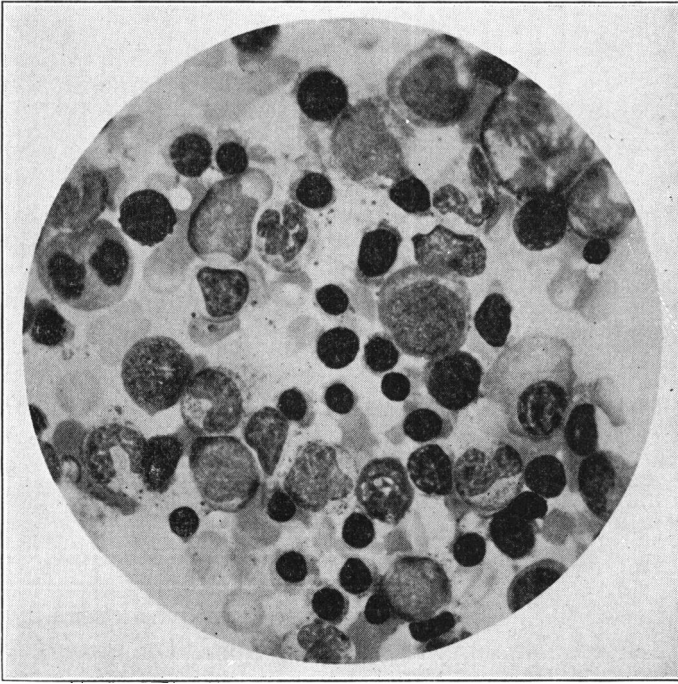


Fig. 3. Smear of Bone-Marrow. Note Numerous Normoblasts, Few Megaloblasts and Mitotic Megaloblasts. Premature and Mature Granulocytes Present. (X 1000).

The blood-platelets may be reduced, normal or slightly increased. Occasionally, in the more profoundly anemic cases, they are markedly reduced (as low as 100,000). The morphology of the platelets is normal.

Bone-Marrow:

An erythroblastic (normoblastic) reaction is characteristic (Fig. 3). This occurs not only in the achlorhydric group, but in the hypochlorhydric and normochlorhydric type. In one case of achlorhydric anemia associated with lues, in which treatment with iron as well as transfusions was unsuccessful, a normo-erythroblastic hyperplasia was found. An unusual finding in this case was also a simple gastric ulcer associated with achlorhydria.

Association with other Conditions:

The occurrence of hemorrhoids, menorrhagia, organic (not malignant) gastric or intestinal lesions, is not infrequent in other disorders. Their presence, however, in cases with achlorhydria, hypochlorhydria, and at times, normochlorhydria, may be a predisposing factor in the early development of the anemia. In fact, some of the well-defined cases of hypochromic anemia have been admitted to the hospital for other conditions. This is well illustrated in one of our recent cases, first seen by a laryngologist for nasal polypi. On admission to the hospital, it was noticed that the patient had an intense pallor and examination of the blood revealed typical hypochromic anemia (hemoglobin 32 per cent, red cells 3,650,000), with complete achlorhydria. With iron treatment, the hemoglobin rose to 67 per cent in four weeks, when the patient had a large number of polypi removed without undue hemorrhage.

In another instance, the patient was first seen by an ophthalmologist for partial amblyopia. On examination, it was observed that the vessels were paler on the disc than they were peripherally, a usual finding in patients with a hemoglobin below 30 per cent. This was confirmed by blood studies of the case (hemoglobin 26 per cent, red cells 2,980,000). After several weeks of iron therapy the eyesight improved with the rise in hemoglobin to 72 per cent.

The presence of any of the following associated conditions may induce or aggravate the severe anemia: (1) menorrhagia; (2) hemorrhoids; (3) pregnancy; (4) lues; (5) intestinal infestation; (6) nasal polypi; (7) hyperthyroidism or hypothyroidism; (8) gastric or duodenal ulcer; (9) improper diet.

The anemia may subside in some cases without particular attention to these complications. In others, however, improvement does not occur until such factors are specifically treated. Rhoads and Castle (31) observed frequent

associations of achlorhydric anemia and ankylostomiasis which improved rapidly on iron medication. Cases in which the hook-worm is eradicated recover rather slowly unless iron is administered. In one of our cases resistant to treatment on account of metrorrhagia, no response to iron was obtained until an hysterectomy had been performed.

Prognosis:

The prognosis in hypochromic anemia, with respect to life is favorable. The syndrome, however, runs a chronic course, and, unless therapy is continued indefinitely, the patient will experience exacerbations of symptoms.

Treatment:

The only successful therapeutic agent available is inorganic iron. Attempts have been made to treat this type of anemia with ventriculin, liver, liver extract, and fetal liver, but have resulted in failure. Our most consistent results have been obtained from the use of iron in dosage of at least ten grains three times a day. Iron ammonium citrate, saccharated carbonate of iron, reduced iron, and Bland's pills have been used with equally favorable results in the dosage indicated. After a week or two on any one of these preparations, the hemoglobin begins to increase and the patients feel and appear better. The reticulocyte count rises, but not to the same degree as after beginning liver therapy in pernicious anemia. On an average, 3 to 8 reticulated cells per hundred erythrocytes can be counted. With respect to the use of copper in addition to the iron, the authors have not found recovery to be any more rapid when added.

In addition to this specific therapeutics, most of our patients are given hydrochloric acid and pepsin. They are placed on a well-balanced, full diet in the hospital, and are urged to continue this diet when they return home. Curiously enough, once improvement has begun, the patient has little or no difficulty in assimilating meats and vegetables, whereas previously these were not tolerated, the diet having been limited to bread and cereals.

The use of iron should be continued almost indefinitely. In analyzing the results, it has been found that steady improvement may be expected while patients are under direct supervision in the hospital. As soon as they are transferred to the Out-Patient Department, there is less tendency to improve. This may be due to (1) laxity in continuing medication, and (2) economic stress, i.e., inability to secure the adequate diet which should complement the iron.

A certain number of cases seem to be resistant to iron, no matter how large an amount is given. These do not seem to respond to any form of therapy now in use, most of them having either neglected their symptoms for years, or having gone through many cycles of remission and exacerbation.

Alterations in the Blood Picture During Treatment:

As iron is almost a specific, continued observation of the blood changes is of great interest. The hemoglobin increases rapidly to almost normal, or slightly below. This increase is much greater than the proportionate increase in the red cells. The red blood-cells increase to the normal number and in some instances may rise to above 6,000,000. The morphology of the red cells shows changes from the beginning. Poikilocytosis soon disappears, anachromasia gives way to the normal or orthochromatic red cells. The color index tends to return to normal. The reticulocytes which are normal at first increase slightly (3 per cent to 8 per cent) within a week.

The size of the red blood-cells shows a tendency to slow recovery to the normal. The microcytosis apparently persists much longer than the other changes.

The volume of packed red cells conforms to the improvement in the clinical condition. As the hemoglobin increases with and without a corresponding increase in red blood-cells, the volume percentage as well as the relative cell volume gradually return to normal. The volume index and mean corpuscular volume also tend to return to normal.

Summary:

1. Simple achlorhydric anemia is a syndrome which occurs most frequently in middle-aged women.
2. The anemia is characterized by microcytosis and low color index.
3. Iron deficiency is probably the underlying factor in the development of the anemia.
4. Certain conditions may be contributory to the development or aggravation of the anemia, such as, uterine hemorrhage, hemorrhoids, intestinal infestations, and nutritional disturbances.
5. Adequate doses of inorganic iron (reduced iron—thirty grains daily) usually act as a specific.

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